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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/256,237	02/24/99	HEIDTMANN H	026083/0195

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EXAMINER	
DAVIS, M	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/256,237	Heidtmann et al
Examiner	**Group Art Unit**
Minh-Tam Davis	1642

☒ Responsive to communication(s) filed on *Nov 30, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *19-25* is/are pending in the application.

Of the above, claim(s) *19, 20, 22, and 24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *21, 23, and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 21, 23, and 25 are being examined.

The following are the remaining rejections.

PRIORITY DATE

The Examiner acknowledges that a copy of the prior application DE 197 01 141.1 is present in the parent application SN=09/008308. A certified, translated copy of DE 197 01 141.1 however has not been found. Therefore, the priority date of 01/16/98 for the instant application remains.

REJECTION UNDER 35 USC 101, NEW REJECTION

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 21, 23 and 25 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 21, 23 and 25 are drawn to a polypeptide and a method of making said polypeptide, wherein said polypeptide is encoded by a nucleic acid construct comprising: a) at least one promoter, linked to b) at least one nucleic acid sequence which encodes an endogenous active compound, which is linked to c) at least one nucleic acid sequence, which encodes an amino acid sequence cleavable specifically by a protease, which is released from a mammalian cell, and which is linked to d) at least one DNA sequence which encodes a polypeptide which is bound to said active compound via said cleavable amino acid sequence, and inhibits the activity of said active compound, and wherein said nucleic acid component c) does not naturally occur as linking to said nucleic acid sequence b) to said nucleic acid d).

The disclosed utilities for the claimed polypeptide are for treating numerous diseases which have an increased local formation of proteases, such as tumors, allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system (p.47-48).

The specification discloses one prophetic example of a nucleic acid construct encoding factor X (component b), wherein its natural cleavage site is replaced by an nucleic acid sequence encoding a prostate specific antigen (PSA)-specific cleavage site (component c). The specification further discloses that the component d) is a naturally occurring precursor of factor X (p.43). The specification also discloses that factor X, when cleaved at its natural cleavage site, will result in coagulation active factor Xa. The specification further discloses that the claimed polypeptide could be used for treating prostate carcinoma metastases, wherein the prostate carcinoma metastases secretes PSA, which is a protease. The specification also discloses other protease cleavage site, beside

PSA-specific cleavage site, such as the sites from plasminogen activator, cathepsin etc.. (p.40-42). The specification discloses beside *in vivo* administration of the claimed nucleic acid construct, *ex vivo* gene transfer of the cells of the subject mammals. However, no specific examples of polypeptides are disclosed in the specification, for use in the treatment of diseases such as allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system.

It is questionable that the claimed polypeptide could be used for treating numerous diseases as claimed. For the claimed polypeptide to function, the claimed polypeptide has to be cleaved by a protease secreted by target cells. It is questionable that there is adequate amount of active protease at the target site to cleave the claimed polypeptide. For example, although there is a high level of prostate specific antigen (PSA) in serum of human patients with prostate cancer, it is well known in the art that most PSA in the serum is inactive, by complexing with a protease inhibitor, ACT, and that although the secreted PSA at the extracellular site of tumor cells is initially active, it could readily form complexes with ACT (Denmeade, SR et al, 1997, of record, p.4929). This type of protease/protease inhibitor complexation in serum or on cell surface is well known in the art and could apply as well to the claimed proteases other than PSA, such as cathepsin, plasminogen activator etc...For example, similar to PSA, cathepsin is also complexed with the protease inhibitor ACT in serum (Wang et al, 1999, Hybridoma, 18(6): 535-41). Similarly, plasminogen activator is inhibited by complex formation with protease inhibitors present in plasma (Haggroth, L et al, 1984, Thrombosis Res, 33(6): 583-94). In addition, a 43 kD irreversible inhibitor of the plasminogen activator is secreted by cardiac monocytes and is found on the surfaces of cultured neurons (Patterson, PH, 1985, J Physiologie, 80(4): 207-11.

Further, as drawn to factor X, it is not clear what compound is precursor of factor X, and by which site of factor X the precursor interact with factor X. It is not clear whether the presence of the precursor, which is presumably a large molecule, and is bound to the PSA-specific cleavage site, a small peptide, would interfere with the activity of PSA in cleaving the PSA-specific cleavage site. It is not clear how and what would trigger the precursor of factor X to be released from factor X, and the inhibition of factor X by its precursor is abolished at the site of tumor. Even if there is adequate amount of activated factor X, i.e. factor Xa, at the site of tumor to induce blood coagulation, it is questionable whether there is adequate blood coagulation to inhibit growth of new blood vessels induced by prostate cancer metastasis. In addition, it is questionable that the claimed polypeptide would be effective in treating cancer, in view of the lack of guidance on necessary dosage and schedule of cancer treatment, and in view of the unpredictability of cancer therapy, as recited by Gura, Jain, Curti, and Hartwell (of record, see pages 6-8 in previous Office action)

The same type of above question applies as well to other contemplated constructs for use in treating allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system. Further, the specification lacks guidance on the necessary dosage and schedule of treatment when using the claimed polypeptide for treating allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system.

In addition, therapeutic agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the target cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient

period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

Moreover, with regard to *ex vivo* use of the claimed polypeptide, it is not clear how cells, that are *ex vivo* transfected with the claimed nucleic acid contruct, could be used for treating numerous diseases which have an increased local formation of proteases, such as tumors, allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system. In addition, the specification lack guidance on the necessary dosage and schedule of treatment when using the cells transfected with the claimed nucleic acid construct for treating tumors, allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 21, 23 and 25 pertaining to lack of enablement for use of the claimed polypeptide remains for reasons already of record in paper No.8.

Applicant argues as follows:

The claims in question do not recite methods of treating cancer. In addition, the claimed nucleic acid construct and the encoded polypeptide can be designed for multiple purposes besides treatment of cancer. The Examiner's lengthy discussion of unpredictability of cancer treatment is misplaced. The specification teaches how to make and use the claimed polypeptide. Although a degree of experimentation is necessary for such use, this experimentation is routine for the field of this invention. With regard to *in vivo* administration, the specification contemplates *ex vivo* administration as well. The specification rely upon well-known and acceptable techniques. Further the law does not require that the results of an experimentation be predictable.

Applicant's arguments set forth in paper No.9 have been considered but are not deemed to be persuasive for the following reasons:

Although the claims do not recite the method of treating cancer, the claimed polypeptide is not enable, because it would be a burden for one skill in the art to use the claimed polypeptide as claimed. The Examiner's discussion of unpredictability of cancer treatment is necessary, because the only example recited in the specification is a construct

comprising Factor X, which was contemplated for use in treating protate tumor metastasis. Further, for the contemplated use of the claimed polypeptides for treating allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system, the same type of question concerning how factor X construct could function applies as well to other contemplated constructs for treating other diseases, *supra*. Further, although the specification discloses well known techniques for how to make the claimed polypeptide, the specification lack guidance on the necessary dosage and schedule of treatment when using the claimed polypeptide for treating cancer, allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system. Moreover, although the law does not require that the results of an experimentation be predictable, but in view of the overwhelming unpredictability of cancer treatment in the art, as recited by several references in prior Office action, such as Gura, Jain, Curti, and Hartwell (of record), one of skill in the art would have questioned the effectiveness of the claimed polypeptide in cancer treatment.

Moreover, it is not clear how cells, that are *ex vivo* transfected with the claimed nucleic acid contruct, could be used for treating numerous diseases which have an increased local formation of proteases, such as tumors, allergies, autoimmune diseases, infections, inflammations, transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system. In addition, the specification lack guidance on the necessary dosage and schedule of treatment when using the cells transfected with the claimed nucleic acid construct for treating tumors, allergies, autoimmune diseases, infections, inflammations,

transplant rejection reactions, thrombosis and blood vessel occlusions, and tissue injuries, including injuries to the central nervous sytem and damage to the nervous system.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph of claims 21, 23, and 25 pertaining to lack of enablement for a polypeptide construct comprising an amino acid sequence cleavable by any protease, which is released by any mammalian cell, remains for reasons already of record in paper No. 8.

Applicant has amended claim 25 by replacing the language "an enzyme" with "a protease". Applicant argues that a variety of proteases are released from different cell types, which could be tumor cells, but also other cells such as endothelial cells, macrophages, lymphocytes, muscle cells, epithelial cells, glia cells, synovial cells and virus infected cells.

Applicant's arguments set forth in paper No.9 have been considered but are not deemed to be persuasive for the following reasons:

The claims read on a polypeptide which could be cleaved by any protease, which is released from any mammalian cells. The claimed polypeptide certainly would be cleaved in the serum by proteases such as trypsin or chymotrypsin etc.., before reaching the target cells, and thus would be useless.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

January 21, 2001